BARNES & THORNBURG LLP

11 South Meridian Street
Indianapolis, Indiana
46204
(317) 236-1313
(317) 231-7433 Fax

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Application No.:	10/074,169
Invention:	AUTOMATED ANALYSIS OF REAL-TIME NUCLEIC ACID AMPLIFICATION
Inventor:	Carl T. Wittwer
Filed:	February 12, 2002
Attorney Docket:	7475-70049
Examiner:	Jeffrey N. Fredman

Certificate Under 37 CFR 1.8(a)

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on March 23, 2006

Rebecca Ball
(Signature)

Rebecca Ball
(Printed Name)

REPLY BRIEF UNDER 37 C.F.R. § 1.193(b)

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

An Examiner's Answer was mailed on January 26, 2006 in the above-captioned application. Appellants hereby submit a Reply Brief under 37 C.F.R. § 1.193(b), in response to the Examiner's Answer. Appellants do not believe that any fees are required with this Reply Brief. If any fees are required, the Commissioner is hereby authorized to charge any fees or credit any overpayment to Appellants' undersigned counsel's deposit account 10-0435 with reference to our matter 7475-70049.

ARGUMENTS

Rejection of Claims 1 and 3-10 for Obviousness-Type Double Patenting and Under § 103(a)

Direct Motivation

The Examiner has rejected claims 1 and 3-10 for obviousness-type double patenting over claims 1-24 of U.S. Patent No. 6,387,621 (the '621 patent) in view of Herrmann et al. The Examiner also rejected claims 1 and 3-10 under 35 U.S.C. § 103(a) over EP 1059523 A2 (Wittwer) in view of Hermann et al. Wittwer is the European counterpart of the '621 patent. The Examiner makes the same substantive arguments for rejecting claims 1 and 3-10 under 35 U.S.C. § 103(a) based on Wittwer in view of Herrmann et al. as the Examiner makes for rejecting claims 1 and 3-10 for obviousness-type double patenting over claims 1-24 of the '621 patent in view of Herrmann et al. The Appellant respectfully traverses the Examiner's rejection of claims 1 and 3-10 for obviousness-type double patenting and under § 103(a). Claims 1 and 3-10 are not obvious over the '621 patent claims in view of Herrmann et al. or over Wittwer in view of Herrmann et al.

The Examiner presents a number of arguments in his Answer not made previously in any of the four office actions issued in this application. Appellant will respond to each of these arguments in the order they are presented in the January 26, 2006 Answer filed by the Examiner.

In his Answer, on page 11, under the heading "Motivation," through page 12, line 1, the Examiner argues that "the combination of the claims of U.S. Patent No. 6,387,621 and Hermann is based upon a simple premise, that Hermann's teaching that temperature melting can be confirmatory of successful or unsuccessful PCR methods is desirably combined with the claims of U.S. Patent No. 6,387,621 to determine whether that method is

successful." The Examiner mischaracterizes the teachings of Herrmann et al. to make this motivation to combine argument.

Although the '621 patent claims are directed to a method for accurately discriminating between ***positive and negative samples*** based on an analysis of the background fluorescence during a PCR reaction to determine whether PCR has been successful or unsuccessful, Herrmann et al. has nothing to do with determining whether PCR has been successful or unsuccessful, but, rather involves ***differentiating between multiple DNA's in a sample*** by the identification and comparison of two or more melting curves, each of which is characteristic of a specific nucleic acid in the sample. Accurate discrimination between positive and negative samples in the context of the '621 patent claims is accomplished ***without analysis or comparison to different signals resulting from different nucleic acids in the sample***. In contrast, melting temperature analysis in the context of Herrmann et al. is used to differentiate between multiple DNA's in a sample by comparing different signals (*i.e.*, different melting curves) specific to different nucleic acids in the sample.

In fact, Herrmann et al. is limited to the use of melting curve analysis in the context of discriminating between multiple DNA's (*i.e.*, multiple signals) in a PCR sample. In this regard, the statements cited by the Examiner in Herrmann et al. that the Examiner argues provide express motivation to combine Herrmann et al. with the '621 patent claims are all directed to using melting temperature analysis to ***discriminate between multiple DNA's in a PCR sample***. The statements in Herrmann et al. pointed to by the Examiner are:

> The ability to multiplex PCR analysis by color and T_m has many uses in addition to multiplex genotyping. For example, internal amplification controls often are needed for infectious disease and translocation testing to verify that amplifiable DNA or cDNA is present even if the target amplification is negative. Another common need is for multiplexing a competitor as an internal standard for PCR quantification.

The statements cited by the Examiner in Herrmann et al. are directed to

discrimination between multiple DNA's 1.) in the context of multiplex genotyping, 2.) in the context of discrimination between an internal amplification control and the target DNA, and 3.) in the context of discrimination between a competitor as an internal standard and the target DNA. These statements in Herrmann et al. are unambiguously limited to the use of melting curve analysis in the context of ***multiplex experiments***. In other words, Herrmann et al. is unambiguously limited to the use of melting temperature analysis to discriminate between multiple DNA's in a PCR sample, not to determine whether PCR has been successful or unsuccessful. The methods described in Herrmann et al. have nothing to do with analyzing background fluorescence to determine whether or not PCR has been successful. Herrmann et al. describes a method for ***differentiating between multiple DNA's in a PCR sample*** by the identification and comparison of two or more melting curves.

The Examiner then states (page 12, lines 1-3) that "Hermann expressly teaches that the temperature melting method can be used as a confirmatory control, as already quoted in the rejection above "The ability to multiplex PCR analysis by color and T_m has many uses in addition to multiplex genotyping. For example, internal amplification controls often are needed for infectious disease and translocation testing to verify that amplifiable DNA or cDNA is present even if the target amplification is negative. Another common need is for multiplexing a competitor as an internal standard for PCR quantification (see page 428, column 1)."" The statements cited by the Examiner do not indicate that melting temperature analysis can be used "as a confirmatory control." As already discussed, these statements simply indicate that melting temperature analysis can be used to discriminate between multiple DNA's in a sample 1.) in the context of multiplex genotyping, 2.) in the context of discrimination between an internal amplification control and the target DNA, and 3.) in the context of discrimination between a competitor as an internal standard and the target DNA.

Moreover, the melting temperature analysis method described in Herrmann et

al. is not taught or described as a "control" as the Examiner contends, but rather the melting curves generated in the method described in Herrmann et al. represent the final data that is obtained in the Herrmann et al. method. The results of the method described in Herrmann et al. are the melting curves, and the melting curve data is used directly to distinguish between DNA's in a sample, based on differentiation between the melting curves of multiple DNA's in a sample. Thus, contrary to the Examiner's assertion, Herrmann et al. does ***not*** teach that "the temperature melting method can be used as a confirmatory control." Furthermore, as discussed above, the statements cited by the Examiner (page 12, lines 3-8 of the Examiner's Answer) do not in any way indicate that melting temperature analysis can be used "as a confirmatory control," but these statements simply indicate that melting temperature analysis can be used to discriminate between multiple DNA's in a sample.

On page 12, line 9 through page 13, line 11, the Examiner relies on two new statements not previously relied on to provide motivation to combine Wittwer and Herrmann et al. The Examiner indicates that the statements that "By multiplexing the probe T_ms and only two colors, we were similarly able to genotype three different point mutations. An additional advantage of using hybridization probes is that unexpected sequence alterations can be detected (see page 428, column 1)" provides motivation to combine melting temperature analysis with confidence band analysis. The Examiner first indicates that "Here Herrman expressly teaches that the melting temperature analysis, T_ms, is combined (multiplexed) with the analysis of two colors to permit multiplexing." Appellant agrees that Herrmann et al. teaches that melting temperature analysis can be used in combination with probes of different colors for multiplex genotyping.

However, the Examiner goes further and suggests that the statement quoted in the preceding paragraph suggests that melting temperature analysis should be combined with confidence band analysis. The Examiner makes this suggestion because "The ability to

genotype multiple different mutations along with the ability to detect unexpected alterations both provide motivation to confirm the fluorescence analysis with the melting temperature analysis of Herrman." The Examiner's analysis does not make sense. The ability to perform multiplex genotyping or to detect unexpected alterations, which is a direct result of multiplex genotyping (*e.g.*, detection of unexpected DNA polymorphisms by detecting multiple DNA's in a sample), by using melting temperature analysis in combination with probes of different colors has nothing to do with establishing a baseline fluorescence region by confidence band analysis.

Again, Wittwer is directed to a method for accurately discriminating between ***positive and negative samples*** based on confidence band analysis of the background fluorescence during a PCR reaction to determine whether PCR has been successful or unsuccessful. The multiplex genotyping method described in Herrmann et al. has nothing to do with determining whether PCR has been successful or unsuccessful, but, rather involves ***differentiating between multiple DNA's in a sample*** by the identification and comparison of two or more melting curves.

The statements that "By multiplexing the probe T_ms and only two colors, we were similarly able to genotype three different point mutations. An additional advantage of using hybridization probes is that unexpected sequence alterations can be detected (see page 428, column 1)," simply say that multiplex genotyping, to identify point mutations or unexpected sequence alterations, can be accomplished using melting temperature analysis in combination with probes of different colors. These statements in no way provide motivation to combine melting temperature analysis with confidence band analysis, a completely different type of analysis than multiplex genotyping.

The Examiner then argues (page 13, lines 1-11) that the statements in Wittwer that "Perhaps the most basic analysis of real time PCR data is a judgment of whether a

targeted nucleic acid is present. If the nucleic acid is present, further quantification and genotyping may take place (see page 6, lines 55-59)" provide direct motivation to perform the melting temperature analysis of Herrmann et al. in combination with the method described in Wittwer. The Examiner makes this argument simply because the statements above from Wittwer refer to genotyping.

The claims of the instant application require the steps of "performing a confidence band analysis on the plot to generate a positive or negative call, and if the call is positive, confirming the positive call by a melting temperature analysis." Therefore, the claims of the instant application require that melting temperature analysis be done directly in connection with confidence band analysis, which does not require any further analytical method step such as multiplex genotyping. Thus, if Herrmann et al. were combined with Wittwer based on a reference to genotyping in Wittwer, the result of the combination would be multiplex genotyping using melting temperature analysis. The issue is not whether the combination of Herrmann et al. and Wittwer suggests genotyping in combination with melting temperature analysis, but, rather whether the references suggest confidence band analysis in combination with melting temperature analysis, as required by the claims of the instant application. Thus, the Examiner's motivation to combine arguments fail because the subject matter combined, based on the Examiner's argument, is not what is claimed.

A similar argument is applicable to the Examiner's statement on page 13, line 19 through page 14, line 2 that "[t]here is strong direct motivation from Hermann to use the melting temperature method to control for variation and to multiplex, particularly in combination with the allelic analysis method of claim 11 of U.S. Patent 6,387,621." Claim 11 implies a further step of genotyping, subsequent to confidence band analysis, but the combination of genotyping and melting temperature analysis is not what is claimed in the instant application. As discussed above, the claims of the instant application require the steps

of "performing a confidence band analysis on the plot to generate a positive or negative call, and if the call is positive, confirming the positive call by a melting temperature analysis." Therefore, the claims of the instant application require that melting temperature analysis be done directly in connection with confidence band analysis, not in connection with any subsequent genotyping step. Based on all of the above arguments, the Examiner has provided no direct motivation to combine the '621 patent claims or Wittwer with Herrmann et al.

Nature of the Problem to be Solved

The Examiner further argues (page 14 and page 15, line 12 through page 16, line 4) that the nature of the "recognized problem" in U.S. Patent No. 6,387,621 lends itself to a solution with Herrmann et al. The Examiner contends that the '621 patent and Wittwer recognize that there are problems with the confidence band analysis method described in the cited references, and that Herrmann et al. provides a solution. The Examiner also contends that Appellant argues that the problem presented in the '621 patent and Wittwer is solved by confidence band analysis so there is no motivation to make improvements.

First, as stated in MPEP § 804.2.B.1., "[a] double patenting rejection of the obvious-type is "analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. 103" except that the patent principally underlying the double patenting rejection is not considered prior art. *In re Braithwaite*, 379 F.2d 594, 154 USPQ 29 (CCPA 1967)." MPEP § 804.2.B.1. Thus, when considering whether the invention defined in a claim of an application would have been an obvious variant of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art. *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1279 (Fed. Cir. 1992). The Examiner is improperly using the disclosure of the '621 patent in the obviousness-type double patenting rejection. The following discussion is directed to the '621 patent in reply to the Examiner's

comments, but each of the statements made here is equally relevant to Wittwer. Again, the Examiner improperly uses the text of the '621 patent in the double patenting rejection.

The Examiner's contentions that 1.) the '621 patent and Wittwer recognize that there are problems with the confidence band analysis method described in the cited references, and that 2.) Appellant argues that the problem presented in the '621 patent and Wittwer is solved by confidence band analysis so there is no motivation to make improvements are incorrect. The statements in the '621 patent that the Examiner points to that "accurately discriminating between positive and negative samples is not easy in practice," and that "[a]utomatic identification of the background is surprisingly difficult" are found in column 6, lines 15-17 and column 6, lines 48-49 of the '621 patent. As discussed on pages 7-10 in the Appeal Brief, filed on December 21, 2005, these statements are made in a section of the '621 patent that discusses problems with prior art methods that had previously been used to attempt to discriminate between positive and negative PCR samples. These statements are in a section of the '621 patent that leads into the specific description in the '621 patent of the steps that are performed to carry out confidence band analysis according to the method described in the '621 patent. This specific description of the steps in the confidence band analysis method described in the '621 patent begins at column 6, line 55 and continues through column 8, line 67. The last statements in this section of the '621 patent are that "[i]f the test point fluorescence is outside of the confidence interval, the sample is positive. If it is within the interval, the sample is negative. FIGS. 7 and 8 are samples which are positive, while FIGS. 9-11 are negative samples." See column 8, lines 64 to 67 of the '621 patent.

The Examiner has taken the statements in the '621 patent that "accurately discriminating between positive and negative samples is not easy in practice," and that "[a]utomatic identification of the background is surprisingly difficult" out of the context in

which those statements are made in the '621 patent. These statements are made in a section of the '621 patent that discusses the problems with prior art methods. These problems are resolved by the confidence band analysis method described in the '621 patent. Thus, the statements pointed to by the Examiner do not suggest that there are problems with the confidence band analysis method described in the '621 patent, but rather that there were problems with prior art methods.

There is no suggestion in the '621 patent that the confidence band analysis method described in the '621 patent has not solved the problem pointed to by the statements that "accurately discriminating between positive and negative samples is not easy in practice," and that "[a]utomatic identification of the background is surprisingly difficult." The Examiner has not pointed to such a statement. Indeed, Appellant respectfully submits that the only suggestion that an additional confirmatory method is needed to verify the results obtained by confidence band analysis is the Examiner's hindsight based on Appellant's own disclosure. It is Appellant's own disclosure in the present application that first suggests that an additional confirmatory method (*i.e.*, melting temperature analysis) may be needed to verify the results obtained by confidence band analysis.

The Examiner further argues that another problem with confidence band analysis is recognized by the statement in the '621 patent that "This algorithm should work well in most cases. However, with the high copy fluorescence curve type (FIG. 3D), the shallowest slope might be found at early cycles (resulting in a correct positive call) or at late cycles (resulting in an incorrect negative call) (see column 7, lines 5-8)." Again, the Examiner takes this statement out of the context in which it is made in the '621 patent because the subsequent statements in the '621 patent (see column 7, lines 9-10 and claims), indicate that the patent addresses this problem.

Moreover, Appellant is not arguing, as the Examiner contends, that there is no

motivation to make improvements simply because the '621 patent has provided a solution to the problems with confidence band analysis that were present in prior art methods. Appellant is arguing that there is no statement in the '621 patent that definitively suggests that the confidence band analysis method described in the '621 patent has not solved the problem addressed in the '621 patent, and the Examiner has not pointed to such a statement. The issue is whether there is any suggestion in the '621 patent that the invention claimed in the '621 patent is unsatisfactory. There is no such suggestion in the '621 patent.

The Examiner further argues (page 15, lines 1-11) that the skilled artisan would have been motivated to improve the accuracy of the method described in Herrmann et al. by using the confidence band analysis method described in Wittwer in the Herrmann et al. method and "retain the melting temperature method as a control." However, contrary to the Examiner's suggestion, the melting temperature analysis method described in Herrmann et al. is not taught or described as a "control" as the Examiner contends, but rather, as discussed above, the melting curves generated in the method described in Herrmann et al. represent the final data that is obtained in the Herrmann et al. method. The results of the method described in Herrmann et al. are the melting curves, and the melting curve data is used directly to distinguish between multiple DNA's in a sample, based on the differentiation between melting curves generated by multiple DNA's in a sample. Thus, the melting temperature method in Herrmann et al. is not described in the context of a "control" although the Examiner attempts to characterize the method in that way. Contrary to the Examiner's assertion, Herrmann et al. does ***not*** suggest retaining "the melting temperature method as a control."

Lastly, the Examiner argues (page 16, lines 5-17) that Herrmann et al. does describe differentiation between a positive and negative call so Herrmann et al. does solve the same problem as solved by the '621 patent claims and by Wittwer. The '621 patent claims

and Wittwer describe a method for accurately discriminating between ***positive and negative samples*** based on an analysis of the background fluorescence during a PCR reaction. Herrmann et al. does ***not*** teach a method for discriminating between positive and negative PCR samples to determine whether PCR is successful or unsuccessful, but, rather teaches ***differentiating between multiple DNA's in a sample***. Clearly, the whole of the teachings of Herrmann et al. are directed to combining the use of probes of different colors with melting temperature analysis to differentiate between multiple DNA's in a sample.

In fact, Herrmann et al. is limited to the use of melting curve analysis in the context of discriminating between multiple DNA's (*i.e.*, multiple signals) in a PCR sample. Herrmann et al. solves a completely different problem (*i.e.*, multiplex genotyping) than is pointed to in the '621 patent (*i.e.*, discriminating between positive and negative samples based on an analysis of background fluorescence). Herrmann et al. is unambiguously limited to the use of melting temperature analysis to perform multiplex genotyping. The whole of the teachings of Herrmann et al. have nothing to do with differentiating between positive and negative calls contrary to the interpretation presented by the Examiner. Thus, the nature of the problem pointed to in the '621 patent claims and Wittwer would not lead a skilled artisan to look to Herrmann et al. for a solution, and there is no motivation to combine these references based on the nature of the problem to be solved.

Rejection of Claims 3, 5, 6, and 9 for Obviousness-Type Double Patenting and Under § 103(a)

In addition to the arguments discussed above, claims 3, 5, 6, and 9 specify establishing the baseline fluorescent region "without the use of an internal standard" (claim 3), obtaining the melting profile "by monitoring fluorescence between extension and denaturation during one of the amplification cycles" (claim 5), obtaining the melting profile

"by monitoring fluorescence between annealing and denaturation during one of the amplification cycles" (claim 6), and obtaining the melting profile "by monitoring fluorescence at temperature increments of greater than 0.1°C" (claim 9). Appellant submits that claims 3, 5, 6, and 9 are patentable for the same reasons as noted above. Also, Appellant wishes to point out that the '621 patent claims, Wittwer, and Herrmann et al. do not provide any teaching or suggestion of the limitation of establishing the baseline fluorescent region "without the use of an internal standard," as recited in claim 3. The Examiner argues that claim 3 of the '621 patent provides an "express" teaching of establishing the baseline fluorescent region "without the use of an internal standard." This is simply not the case. The method of claim 3 of the '621 patent could be performed with or without the use of an internal standard and there is simply no teaching, express or otherwise, of performing the method described in claim 3 of the '621 patent "*without the use* of an internal standard."

Claim 5 of the instant application requires obtaining the melting profile "by monitoring fluorescence between extension and denaturation during one of the amplification cycles," and claim 6 requires obtaining the melting profile "by monitoring fluorescence between annealing and denaturation during one of the amplification cycles." The Examiner contends that the fact that Herrmann et al. teaches performing the method subsequent to amplification suggests the embodiments of claims 5 and 6. The simple teaching of performing the method subsequent to amplification suggests neither the embodiment of claim 5 nor claim 6.

Claim 9 requires obtaining the melting profile "by monitoring fluorescence at temperature increments of greater than 0.1°C." The Examiner argues that the disclosure in Herrmann et al. of monitoring fluorescence "at 0.1°C/second" (page 427, column 1) encompasses "monitoring at longer increments." Herrmann et al. provides no such suggestion of "monitoring at longer increments" and the Examiner has not pointed to such a

statement in Herrmann et al. Herrmann et al. simply states that the temperature is raised "at 0.1°C/second." This statement in Herrmann et al. does not provide any suggestion of "monitoring fluorescence at temperature *increments of greater than 0.1°C*" as claimed in claim 9. The Examiner is reading language into Herrmann et al. that does not exist in Herrmann et al. when the Examiner suggests that raising the temperature "at 0.1°C/second" means "monitoring fluorescence at temperature increments of greater than 0.1°C."

CONCLUSION

Accordingly, Appellant submits that the Examiner's rejections of claims 1 and 3-10 for obviousness-type double patenting and for obviousness under 35 U.S.C. §103(a) are clearly erroneous. Appellant urges that the Board reverse the Examiner's rejections. Such action is respectfully requested.

Respectfully submitted,

Rebecca Ball

Rebecca L. Ball
Attorney Reg. No. 46,535
Attorney for Appellant

Indianapolis, Indiana
(317)231-7511